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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/802,376	03/09/2001	Gary Van Nest	377882001700	8397

25226 7590 10/17/2005

MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 10/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/802,376	NEST ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-66* is/are pending in the application.

4a) Of the above claim(s) *3,4,12-55,58 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-11,56,57,60-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-2-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 8-17-05.

Claims 1-66 are pending in the instant application. Claims 1, 2, 5-11, 56, 57, 60-66 have been examined on the merits as set forth below. Claims 3, 4, 12-55, 58 and 59 have been withdrawn as being drawn to non-elected inventions.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 1, 2 and 5-11 are rejected under 35 U.S.C. 102(e) as being anticipated by Raz et al for the reasons of record set forth in the Office action mailed 4-12-05.

Raz et al (USPN 6,589,940) teach pharmaceutical compositions (and kits) comprising an immunomodulatory polynucleotide which comprises the ISS sequence of SEQ ID NO: 1 (which comprises the sequence 5'-T-C-G-3', and which comprises the motif 5'-puring, purine, C,G,pyrimidine, pyrimidine, C,G-3'), and which polynucleotide is covalently attached to a non-biodegradable, solid microcarrier between 10nm and 10um in size, and which ISS-microcarrier complex is optionally antigen-free (*see* accompanying sequence alignment data between SEQ ID NO: 1 of the instant

application and SEQ ID NO: 2 from USPN 6,589,940; *see also* the abstract, col. 14, lines 50-67; col. 15, lines 31-41; col. 17, lines 10-28; col. 20, line 61-col. 21, line 46; col. 27, lines 19-36).

Applicant's arguments filed 8-17-05 have been fully considered but they are not persuasive. Applicant argues that Raz does not anticipate the claimed invention because, particularly in col. 16, Raz teaches microparticles and/or liposomes that encapsulate an ISS-IMM with the claimed sizes. Therefore, according to Applicant, Raz does not teach each and every claimed element of the instant invention. Applicant is correct that, in col. 16, Raz discusses encapsulated microparticles and/or liposomes. But, contrary to Applicant's assertions, the Raz patent is not limited to encapsulated microparticles and/or liposomes. Raz specifically states that embodiments other than encapsulation are disclosed (see col. 16, lines 34-36). Raz also teaches the covalent linkage of non-encapsulated ISS oligonucleotides to platform molecules, and including on the surface of platform molecules (see col. 16, lines 32-41; see also col. 20, line 62-col. 21, line 67). Raz also teaches the covalent linkage of ISS oligonucleotides to an assortment of microcarrier polymers including, but not limited to dextrans, polyols and polyvinyls (see e.g. col. 17, lines 10-28). Applicants also argue that the sizes of the instantly claimed microcarrier complexes (*e.g.* less than about 10um) are not taught by Raz. Contrary to Applicant's assertions, the sizes disclosed by Raz (*e.g.* in the molecular range between 200 and 200,000 as disclosed in col. 21, lines 3-24) encompass the structural limitations of the instantly claimed invention. See In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the

claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112, citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re Best 195 USPQ 430 as per above. Therefore, it falls to Applicant to determine and provide evidence that the compositions disclosed by Raz would or would not have the claimed size limitation (less than about 10um).

Therefore, absent evidence to the contrary, claims 1, 2 and 5-11 are anticipated by Raz et al.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 56, 57 and 60-66 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro immunomodulation of mouse splenocytes and human PMN cells using the IMP/MC complexes of examples 1-4 of the instant specification, does not reasonably provide enablement for compositions and instructions to use any nonbiodegradable IMP/MC complexes for administration and immunomodulation in an individual. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions comprising any immunomodulatory polynucleotide covalently linked to any solid nonbiodegradable microcarrier complex (IMP/MC) and instructions for their administration and immunomodulation in an individual.

The state of the prior art and the predictability or unpredictability of the art.

Crooke points out that cell culture examples are generally not predictive of in vivo efficacy. The concentrations achievable in vitro, and which provide a desired biological effect in a test tube or in cell culture, are not necessarily those easily achieved in vivo. The correlation between in vitro results and in vivo efficacy require undue experimentation (*see e.g.* S. Crooke, Antisense Res. and Application, Chapter 1, pp. 1-50, especially at 34-36, 1999). Likewise, Peracchi generally cautions investigators about the problems of achieving in vivo efficacy based on in vitro approaches. Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy (*see* A. Peracchi et al, Rev. Med. Virol., 14: 47-64, especially at 51, 2004).

Agrawal et al (S. Agrawal et al., Molecular Med. Today, 6: 72-81 at 80, 2000) also speak to the unpredictability in going from in vitro to in vivo to determine biological effects. In addition, Stayton et al discuss the "[k]ey delivery challenges" that "remain before many... therapeutics reach the clinic." An important barrier that persists in successfully extrapolating from in vitro to in vivo is the effective targeting of drugs to specific tissues and cells in concentrations required to achieve a desired biological effect (*See* Stayton et al, J. Controlled Release, 65: 203-220, 2000, at pages 203-204).

The prior art has shown that encapsulation of oligonucleotides enhances resistance of the oligonucleotides to nuclease degradation (*see* Gold et al, USPN 6,465,188, Oct. 15, 2002, at col. 4, line 58-col. 5, line 27; *see also* Kasid et al, USPN 6,559,129, May 6, 2003 at col. 21-23). Collins (USPN 6,355,267, Mar. 12, 2002) and Kasid et al (USPN 6,559,129, May 6, 2003) teach methods of encapsulating polynucleotides for in vitro and in vivo application. Kasid et teach, for instance, efficient encapsulation of nucleotides in cationic liposomes comprising DDAB:phosphatidylcholine and cholesterol most preferably at 1:3.2:1.6, respectively, whereby the lipids are first dissolved in solvent, evaporated to dryness, hydrated, then the nucleotide is added, and the solution is vigorously vortexed and sonicated, and the non-encapsulated oligonucleotides are then removed (see Kasid at col. 7-8, col. 10). Collins teaches the batch to batch variation in liposome preparation methods, leading to compositions comprising encapsulated and unencapsulated molecules associated with liposomes of varying lipid content (e.g. see Collins at col. 3 and 7). Collins also teaches efficient encapsulation of polynucleotides under conditions of strictly defined lipid

compositions, comprising combining the lipids, drying and desiccating the lipid mixture, then hydrating at a temperature above the chain melting temperature of the distearoyl-phosphatidylcholine mixture, microfluidizing the sample and removing the unencapsulating material by ultracentrifugation (see Collins at col. 7-11). The art is silent, however, regarding the immunomodulatory effects of pharmaceutical compositions comprising the broad genus comprising any solid phase and liquid phase nonbiodegradable microcarriers and IMP/MC complexes in an individual.

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of providing compositions comprising any nonbiodegradable IMP/MC compositions in a subject, including those comprising the broad genus encompassing any nonbiodegradable solid phase microcarriers covalently linked to an ISS. The specification teaches the generation of oil in water emulsion comprising an immunomodulatory oligonucleotide covalently linked to cholesterol, and further comprising homogenization of a mixture comprising squalene, sorbitan trioleate,and Tween80; the generation of a mixture comprising and immunomodulatory oligonucleotide and sulphate derivatized polycarbonate microparticles; the generation of immunomodulatory oligonucleotides covalently linked to (e.g. amino derivatized) polystyrene beads. The specification also teaches the immunomodulation of mouse spleen cells and human PMN cells in vitro following administration of these IMP/MC compositions. The specification fails to teach the administration of any IMP/MC to a subject for treatment. The specification fails to teach pharmaceutical compositions

comprising adequate species representing the broad genus drawn to these solid, nonbiodegradable IMP/MC complexes. One skilled in the art would not accept on its face the examples given in the specification of the in vitro immunomodulation of mouse splenocytes or human PMN cells, using the particularly described IMP/MC of examples 1-4 of the instant specification, as being correlative or representative of the administration of pharmaceutical compositions comprising any species encompassed within the broad genus comprising solid, nonbiodegradable IMP/MC's in a subject for immunomodulation. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo administration of the compositions claimed.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions comprising immunomodulatory polynucleotides covalently linked to any solid, nonbiodegradable microcarrier complex (IMP/MC) and instructions for their administration and subsequent immunomodulation in a subject. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of the ability to administer to a subject an adequate representation of species encompassed by the broad genus comprising these solid, nonbiodegradable IMP/MC compositions, and further whereby immunomodulation is achieved in a subject. Since the specification fails to provide any particular guidance for the administration of this broad genus in a subject, whereby immunomodulation is achieved, it would require undue experimentation to practice the invention over the scope claimed.

Conclusion

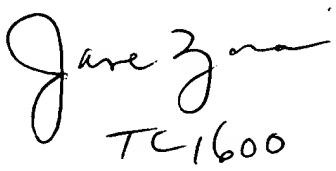
Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
10-13-05



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VERSION     AR287741.1  GI:31674761
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REFERENCE   1  (bases 1 to 22)
  AUTHORS   Raz,E., Cho,H.J., Richman,D. and Horner,A.A.
  TITLE     Methods for increasing a cytotoxic T lymphocyte response in vivo
  JOURNAL   Patent: US 6534062-A 1 18-MAR-2003;
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VERSION     AR287743.1  GI:31674763
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  AUTHORS   Raz,E., Cho,H.J., Richman,D. and Horner,A.A.
  TITLE     Methods for increasing a cytotoxic T lymphocyte response in vivo
  JOURNAL   Patent: US 6534062-A 3 18-MAR-2003;
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VERSION     AR308057.1  GI:31698950
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SOURCE      Unknown.
  ORGANISM  Unknown.
            Unclassified.
REFERENCE   1  (bases 1 to 22)
  AUTHORS   Raz,E., Kornbluth,R., Catanzaro,A., Hayashi,T. and Carson,D.
  TITLE     Immunomodulatory polynucleotides in treatment of an infection by an
            intracellular pathogen
  JOURNAL   Patent: US 6552006-A 1 22-APR-2003;
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VERSION     AR352573.1  GI:33757824
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  ORGANISM  Unknown.
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REFERENCE   1  (bases 1 to 22)
  AUTHORS   Raz,E., Roman,M. and Dina,D.
  TITLE     Immunostimulatory oligonucleotides, compositions thereof and
            methods of use thereof
  JOURNAL   Patent: US 6589940-A 2 08-JUL-2003;
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ORIGIN

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VERSION     AR383158.1  GI:40092605
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            Unclassified.
REFERENCE   1  (bases 1 to 22)
  AUTHORS   Carson,D.A., Raz,E. and Roman,M.
  TITLE     Immunostimulatory polynucleotide/immunomodulatory molecule
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